Early acute kidney injury in military casualties

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BACKGROUND:	While acute kidney injury (AKI) has been well studied in a variety of patient settings, there is a paucity of data in patients injured in the course of the recent wars in Iraq and Afghanistan. We sought to establish the rate of early AKI in this population and to define risk factors for its development.
METHODS:	We combined the results of two studies performed at combat support hospitals in Afghanistan. Only US service members who required care in the intensive care unit were included for analysis. Data on age, race, sex, Injury Severity Score (ISS), first available lactate, and requirement for massive transfusion were collected. Univariate analyses were performed to identify factors associated with the subsequent development of early AKI. Multivariable Cox regression was used to adjust for potential confounders.
RESULTS:	The two observational cohorts yielded 134 subjects for analysis. The studies had broadly similar populations but differed in terms of age and need for massive transfusion. The rate of early AKI in the combined cohort was 34.3%, with the majority (80.5%) occurring within the first two hospital days. Patients with AKI had higher unadjusted mortality rates than those without AKI (21.7% vs. 2.3%, $p < 0.001$). After adjustment, ISS (hazard ratio, 1.02; 95% confidence interval, 1.00–1.03; $p = 0.046$) and initial lactate (hazard ratio, 1.16; 95% confidence interval, 1.03–1.31; $p = 0.015$) were independently associated with the development of AKI.
CONCLUSION:	AKI is common in combat casualties enrolled in two prospective intensive care unit studies, occurring in 34.3%, and is associated with crude mortality. ISS and initial lactate are independently associated with the subsequent development of early AKI. (*J Trauma Acute Care Surg*. 2015;78: 988–993. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)
LEVEL OF EVIDENCE:	Prognostic and epidemiologic study, level III.
KEY WORDS:	Acute kidney injury; trauma; war; lactate; Injury Severity Score.

A cute kidney injury (AKI) is commonly found in critically ill patients requiring admission to the intensive care unit (ICU).[1–3] Even small decrements in renal function have been shown to be associated with an increased risk of morbidity and mortality in a wide variety of patient populations.[4,5] Critically ill trauma patients in particular seem to be at increased risk of developing AKI from multiple mechanisms including hemorrhagic shock resulting in ischemia, direct organ injury, rhabdomyolysis, acute traumatic coagulopathy, disseminated intravascular coagulation, and compartment syndrome.[6]

With the use of standardized definitions,[7–9] a number of recent studies have evaluated the incidence of AKI in a variety of trauma populations and found variable rates from 6% to 50%.[10–15] While the association of AKI with mortality has not been uniformly seen,[13] the preponderance of evidence suggests a correlation between AKI and mortality in the trauma population.[10–12,14,15] Indeed in the setting of trauma, AKI has been referred to as "the canary in the coal mine" because it is a harbinger of adverse outcomes and has been found to be a stronger predictor of multiorgan failure and death compared with hepatic, cardiac, or pulmonary dysfunction.[16] Furthermore, it is increasingly recognized that an episode of AKI is associated with a poor long-term prognosis, to include mortality, the development of chronic kidney disease, and the need for long-term dialysis.[17–22] However, there is a paucity of data on AKI in the current conflicts in Iraq and Afghanistan.

We hypothesized that AKI is common in patients with combat injury and is associated with mortality. To test this hypothesis, we performed a post hoc analysis of two prospectively enrolled cohorts admitted to two different combat support hospitals in Afghanistan.

PATIENTS AND METHODS

Two separate prospective observational studies conducted in Afghanistan were combined to derive our study population. Both studies were approved by the institutional review board

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1. REPORT DATE **01 MAY 2015**	2. REPORT TYPE **N/A**	3. DATES COVERED **-**

4. TITLE AND SUBTITLE **Early acute kidney injury in military casualties**	5a. CONTRACT NUMBER
	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S) **Heegard, K. D.; Stewart, I. J.; Cap, A. P.; Sosnov, J. A.; Kwan, H. K.; Glass, K. R.; Morrow, B. D.; Latack, W.; Henderson, A. T.; Saenz, K. K.; Siew, E. D.; Ikizler, T. A.; Chung, K. K.;**	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **United States Army Institute of Surgical Research, JBSA Fort Sam Houston, Tx 78234**	8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release, distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT **SAR**	18. NUMBER OF PAGES **6**	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**			

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std Z39-18

responsible for studies performed in theater (the US Army Medical Research and Materiel Command). The first cohort, from the damage-control resuscitation (DCR) protocol, was part of a prospective observational study of patients presenting with traumatic injury at Craig Joint Theater Hospital, Bagram Airfield (BAF), and Kandahar NATO Hospital, Kandahar Airfield, from January 2012 to June 2013. Patients were included in this study if they were locally triaged into the most severe category of trauma. Patients admitted more than 24 hours after injury and patients who were not part of coalition forces were excluded. For the purposes of this analysis, only US service members who required ICU-level care were included. The second cohort, from the Urinary Biomarker (UB) protocol, was admitted to BAF from October 2012 to December 2013. Included in this study were US service members with traumatic injury, who were injured within 48 hours of admission, had a Foley catheter, and required ICU-level care. Age, race, sex, mechanism of injury, Injury Severity Score (ISS),[23] first available lactate, and data on massive transfusion requirement (defined as >10 U of red blood cells [RBCs] within 24 hours) was collected in a retrospective or prospective fashion depending on the data element and protocol. The first available lactate was recorded from the larger medical facilities in Afghanistan but was unavailable from earlier in the combat evacuation chain.

For the purposes of this study, we defined early AKI in our study population as the development of a new diagnosis of AKI within 14 days of admission to a combat support hospital in Afghanistan. Levels of serum creatinine were collected for up to 14 days and were available in both Afghanistan and later in the evacuation chain (Germany and the United States). AKI was determined using the criteria outlined in the KDIGO guidelines,[24] which are summarized in Table 1. Baseline creatinine was established by reviewing electronic medical records for a 1-year period before the date of injury. If the patient did not have a baseline creatinine, then a baseline creatinine was derived using the Modification of Diet in Renal Disease (MDRD) study equation assuming a glomerular filtration rate of 75 mL/min per 1.73 m^2.[25] The lower value of this estimated creatinine or the admission creatinine was used as the baseline for AKI determination. We opted to use derived creatinine or the admission creatinine, in place of the lowest value in the first 7 days, because of the high rates of amputations in this patient population, which may lower creatinine independent of renal function.[26] Data on urine output was not uniformly available and thus was not used to determine AKI. Stage 1 or greater AKI was used when stage was not explicitly stated.

Analyses were performed using χ^2 test to evaluate association between categorical variables such as AKI, study, sex, and mass transfusion. For normally distributed continuous variables, a Student's t test was used, while a Wilcoxon U-test was used for variables that were not normally distributed. Because the development of AKI is time dependent and requires that a creatinine be drawn to make the diagnosis, we chose to model risk of AKI using Cox proportional hazard regression. Accordingly, patients were censored on the day of AKI (defined as stage ≥ 1) or the last day that a creatinine was measured. To adjust for confounders, we then used stepwise multivariable Cox proportional hazard regression with an entry criterion of $p < 0.1$ in the univariate analysis. Statistical significance was then

considered as a $p < 0.05$. We did a full case analysis (which excluded two patients without a lactate) for the multivariate model. To test the assumptions of the model, we analyzed the cumulative sums of martingale-based residuals (empirical score process).[27,28] We also modeled mortality using a χ^2 test and a Cox proportional hazard regression, but given the low number of events and the risks of multiple testing, we only examined the effect of AKI.

RESULTS

During the study period for the UB trial, 126 patients were admitted to the ICU at BAF. Of these, 36 patients were excluded (21 did not have a Foley catheter, 7 were injured >48 hours before admission, 4 declined enrollment, 2 were anuric, and 2 were admitted without the investigators being informed). One patient also subsequently withdrew consent, leaving 89 study subjects.

During enrollment for the DCR trial, 85 patients met inclusion criteria. Of these, 3 patients had inadequate data collection, 20 were not US service members, and 16 were not admitted to the ICU, leaving 46 patients. One patient was enrolled in both studies, and the data from this patient were only included in the analysis once (considered as part of the UB cohort). Combining these two cohorts provided a total of 134 subjects for analysis.

Patient characteristics are summarized in Table 2. Both cohorts were almost exclusively male (97.8%), and a small portion (6.0%) of the patients were African American. There was a statistically significant difference in age, with the DCR cohort being slightly younger compared with the UB cohort at (24.5 [3.4] vs. 26.9 [5.3], respectively; $p = 0.006$). In addition, patients in the DCR cohort were also more likely to have required a massive transfusion (55.6% vs. 37.1%) when compared with the UB cohort ($p = 0.042$). However, other variables including ISS, initial lactate, AKI, and mortality were not significantly different between the two groups.

In both cohorts, there was a high rate of early AKI (stage ≥ 1), with 37.1% of the patients in the UB cohort and 28.8% of the patients in the DCR cohorts meeting diagnostic criteria. The rate of AKI in the combined cohort was 34.3%. Both cohorts demonstrated that AKI was predominantly diagnosed on the first or second hospital day, with relatively few (19.6%) diagnosed after hospital Day 2 (Fig. 1). Of the 46 subjects with AKI in the combined cohorts, 34 were KDIGO 1

TABLE 1. Kidney Disease Improving Global Outcomes Criteria for AKI

Stage	Serum Creatinine	Urine Output
1	1.5–1.9 times the baseline value or ≥0.3 mg/dL increase*	<0.5 mL/kg/h for 6–12 h
2	2.0–2.9 times the baseline value	<0.5 mL/kg/h for ≥12 h
3**	≥3 times the baseline value or increase in serum creatinine to ≥4.0 mg/dL†	<0.3 mL/kg/h for ≥24 h or anuria for ≥12 h

*A 0.3 mg/dL rise from admission value must occur within 48 hours, relative increase in baseline must occur (or presumed to have occurred) over 7 days.

**Patients who require RRT for any reason are classified as Stage 3.

†Absolute rise to 4.0 mg/dL or greater assumes diagnosis of AKI by other criteria (e.g., 0.3-mg/dL increase)

TABLE 2. Baseline Characteristics

Variable	UB Cohort	DCR Cohort	Combined Cohorts	p*
Number	89	45	134	—
Age, y	326.9 (5.3)	24.5 (3.4)	26.1 (4.9)	0.006
Male, %	96.6	100	97.8	0.213
African American, %	7.9	2.2	6.0	0.193
ISS, median (IQR)	18 (11–38)	22 (16–29)	21 (14–34)	0.783
Lactate, median (IQR)	1.8 (1.1–2.9)	2.0 (1.3–3.3)**	1.9 (1.2–2.9)	0.351
Massive transfusion, %	37.1	55.6	43.3	0.042
AKI classification, %				0.346
KDIGO 1	25.8	24.4	25.4	
KDIGO 2	4.5	2.2	3.7	
KDIGO 3	6.7	2.2	5.2	
Total AKI	37.1	28.9	34.3	
Day of AKI diagnosis, %				
Day 1	51.5	53.8	52.2	
Day 2	30.3	23.1	28.3	
>Day 2	18.2	23.1	19.6	
Mortality, %	10.1	6.7	9.0	0.509

*p value compares UB and DCR cohorts.
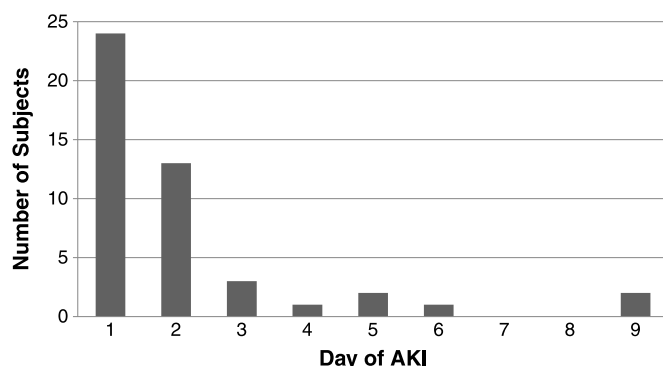**Excludes two patients without data on lactate.
Data are expressed as mean (SD).
IQR, interquartile range.

TABLE 3. Univariate Cox Proportional Hazard Regression for AKI

Variable	HR	95% CI	p
Study	1.33	0.70–2.52	0.389
Age	1.04	0.98–1.09	0.197
Massive transfusion	2.10	1.16–3.77	0.014
ISS	1.02	1.01–1.04	0.001
Initial lactate	1.24	1.12–1.38	<0.001

HRs reflect per unit change in year, ISS, and initial lactate.

(25.4%), 5 were KDIGO 2 (3.7%), and 7 (5.2%) were KDIGO 3. Only one patient (from the UB cohort) required renal replacement therapy (RRT) in Afghanistan. Data on the need for RRT further up the evacuation chain was only available for the UB - cohort. In this cohort, an additional five patients required RRT in Germany.

The univariate analysis for factors associated with the development of AKI in the combined cohort is shown in Table 3. Massive transfusion (hazard ratio [HR] 2.10; 95% confidence interval [CI], 1.16–3.77; $p = 0.014$), ISS (HR, 1.02; 95% CI, 1.01–1.04; $p = 0.001$), and initial lactate (HR, 1.24; 95% CI, 1.12–1.38; $p < 0.001$) were significantly associated with AKI, while age and study (DCR vs. UB) were not. The effect of sex could not be modeled because there were only three female subjects and race was likewise not modeled.

In the multivariable analysis (Table 4), ISS (HR, 1.02; 95% CI, 1.00–1.03; $p = 0.046$) and initial lactate (HR, 1.16;

95% CI, 1.03–1.31; $p = 0.015$) were independently associated with the development of AKI. Rerunning the model with an interaction between ISS and lactate showed that there exists a positive interaction, implying that the positive correlation of ISS with AKI may be nonlinear at different levels of initial lactate and vice versa (data not shown).

Of the 12 patients who died in the combined cohorts, 10 had AKI. This resulted in a mortality rate of 21.7% for patients with AKI and 2.3% for patients without AKI ($p < 0.001$). On univariate Cox proportional hazard regression model, AKI was highly associated with subsequent mortality (HR, 4.07; 95% CI, 2.00–8.31; $p < 0.001$). This relationship is unadjusted for known confounders between the relationship of AKI and mortality and therefore should be interpreted with caution.

DISCUSSION

In an effort to estimate the incidence of AKI and identify risk factors associated with its development in critically injured US service members, we combined two separate cohorts of patients admitted to combat support hospitals in Afghanistan. Despite minor differences between the two cohorts (age and the need for massive transfusion), they had a similar incidence of AKI and mortality. When combined, the two cohorts had an overall rate of AKI of 34.3%, with the majority occurring in the first two hospital days (80.5%). We also found that ISS and initial lactate were independently associated with AKI.

Previous studies of AKI in trauma patients have shown variable rates ranging from 6% to 50%.[10–15] This wide range may reflect differences in patient populations, the definition of AKI used (RIFLE [Risk, Injury, Failure, Loss and End-stage kidney disease] vs. AKIN [Acute Kidney Injury Network]), the methods used to estimate baseline creatinine, or variable use of the urine output criteria. While AKI has been examined in past conflicts from the World War II to the Vietnam War, there is a paucity of data in the current conflicts using modern definitions of AKI. In World War II, analysis of 186 patients with "severe

Figure 1. Hospital day of AKI diagnosis.

TABLE 4. Multivariable Cox Proportional Hazard Regression Model for the Development of AKI

Variable	HR	95% CI	p
ISS	1.02	1.00–1.03	0.046
Initial lactate	1.16	1.03–1.31	0.015

HRs reflect per one unit change in year, ISS, and initial lactate.

wounds" demonstrated an AKI rate of 42.5% (defined by either anuria or blood urea nitrogen ≥ 65 mg/dL).[29] The mortality in the AKI group was 64.6% compared with 13.1% in the non-AKI group. In the Korean War, oliguric AKI occurred in 0.5% of all combat casualties and was associated with an increase in mortality from 5% to 90%.[30] The first description of RRT in the treatment of combat-associated AKI was in the Korean War.[31] This work found a decrease in the mortality of oliguric patients from 90% to 68% following the introduction of the Brigham-Kolff artificial kidney. In Vietnam, one small study examined early (blood urea nitrogen < 70 mg/dL) versus late (>150 mg/dL) initiation of RRT. In this study, mortality rates were 36% in the early group and 80% in the late group. In the current conflicts, modern definitions for AKI have only been examined in patients that experienced a burn injury in support of combat operations in Iraq and Afghanistan. This work found the incidence of AKI to be 23.8% and 29.9% by the RIFLE and AKIN criteria, respectively.[32]

We found that of the 46 patients in the combined cohort with AKI, there were 10 deaths (21.7%) compared with only 2 deaths in the 88 patients who did not develop AKI (2.3%). This mortality rate of 21.7% in patients with AKI is comparable with the rates of 14.9% to 57% found in other trauma populations.[10–12,14,15] While AKI was strongly associated with mortality on the univariate analysis, we did not have a sufficient number of events to examine factors associated with mortality in a multivariable model. These results should therefore be interpreted with caution because we could not adjust for other factors associated with mortality.

The combined cohort demonstrated a statistically significant association between ISS and development of AKI. The median ISS of 21 indicates severe injury among the patients in the cohort, with the patients that developed AKI having a higher median ISS (29.5) when compared with those who did not develop AKI (18). While an association between ISS and AKI has been observed before,[13] the majority of other studies examining this relationship in the trauma population have failed to show a similar correlation.[11,12,14,15] It is possible that baseline characteristics between our population and these other cohorts could explain these disparate findings. While the median ISS in our study is comparable, our study population is younger. The mean age in our study was 26.1 years compared with an average age of approximately 40 years in the bulk of the work cited earlier. Older patients have higher rates of comorbidities, such as diabetes and hypertension, which may predispose to AKI even in the absence of severe injury. Therefore, our study is subject to less confounding and may be able to better define the effect of injury severity on the subsequent risk of AKI. Another possibility relates to our findings of a positive interaction of lactate and ISS. This suggests that the different models used in previous work may impact their conclusions.

Elevated initial lactate was also correlated with the development of AKI in the combined cohort. Previous work has shown that increased lactate, whether from trauma or sepsis, is associated with AKI.[11,33] Lactate is a marker for hypoperfusion, ischemia, and underresuscitation, all of which can result in AKI. This should also be understood in the context of current doctrine, in place at the time of these studies, which calls for permissive hypotension (approximately 90 mm Hg) in combat

casualties without central nervous system injury in an effort to avoid dislodging established blood clotting.[34] It should also be noted that this association may not be causal. Under normal physiologic circumstances, the kidney contributes to the removal of up to 30% of an exogenous lactate load.[35] AKI may therefore result in an impaired ability to remove lactate.

Previous studies have also examined the correlation between blood products and AKI in trauma and found an increased risk.[11,14] What is less clear however is whether it is the transfusion itself or the requirement for the transfusion that predisposes to AKI. Shashaty et al.[14] found an increased risk of AKI with blood transfusion, a risk that increased further if the RBCs were unmatched, but the study did not address massive transfusion. Another study found that blunt trauma patients with AKI required a median of 10 U of RBCs compared with 5 U in those who did not develop AKI.[11] From a pathophysiologic standpoint, it seems logical that massive transfusion could be both causative or collinear with the development of AKI. Massive transfusion may exacerbate the systemic inflammatory response syndrome typically seen in trauma resulting in cytokine-mediated direct nephrotoxicity.[36] In addition, massive transfusion may be a marker for hypovolemia, poor perfusion, and renal ischemia. While massive transfusion was associated with AKI in the univariate analysis, our study failed to show an independent relationship between massive transfusion and AKI in the multivariate model.

Our study had several limitations. First, despite our attempt to make the cohorts comparable, we combined two different studies with different inclusion/exclusion criteria that were conducted by different investigative teams in an austere environment. This may have introduced bias; however, given the paucity of prospective data from this unique population, it was necessary to establish an estimate for the incidence of AKI. In addition, the cohorts were small, which impaired our ability to fully examine mortality as an end point. Our study population is also unique and may not be generalizable to the trauma population as a whole. Military casualties tend to be younger, have fewer comorbidities, and are overwhelmingly male compared with the general trauma population. However, the absence of confounding comorbidities, such as diabetes and chronic kidney disease, allows us to more adequately examine the specific effects of trauma on the risk for AKI. The majority of patients (91%) did not have an established baseline, and a baseline creatinine was derived from either a back-calculated value (assuming a glomerular filtration rate of 75 mL/min) or the admission creatinine. While these are useful surrogates in epidemiologic studies, back-calculated creatinine must be interpreted with some caution because it has been shown to misclassify AKI compared with measured serum creatinine.[37] However, previous work has demonstrated that this method is reasonable in younger, nonchronic kidney disease cohorts.[38] We also only had complete data on RRT only for one of the two studies. While this may have resulted in misclassification, it is unlikely to have impacted the overall rate of AKI. Prehospital data to include fluid management, blood transfusion, and blood pressures were not recorded. While these factors could elucidate AKI risk after combat injury, they are variably recorded in this setting. Furthermore, there may be a variable time lag between injury and evacuation to the larger medical facilities (where lactate was recorded).

However, this is the only best lactate data available in war fighters injured in Afghanistan. Lastly, the observational nature of the cohorts does not allow us to infer causation.

In conclusion, early AKI as defined by KDIGO, is common among military casualties enrolled in two prospective ICU studies, occurring in 34.3%. ISS and lactate are independently associated with an increased risk of AKI. With the increased risk in morbidity and mortality associated with AKI in trauma, further investigation is needed to fully elucidate risk factors for AKI and their pathophysiology.

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